Atrial fibrillation and QT prolongation after a single dose of hydroxychloroquine

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SUMMARY
Non-antiarrhythmic drugs may induce QT-prolongation and increase the risk of arrhythmias. Recent studies have determined that there is a risk of atrial fibrillation (AF) due to QT prolongation. We report a case of FA associated to QT prolongation secondary to a single dose of hydroxychloroquine (HCQ) in an 83-years-old polymedicated patient admitted to our hospital due to SARS-CoV-2 infection. Quetiapine was prescribed as regular medicine after admission and a 5-days oral HCQ regimen was started for COVID-19. Thirty minutes after HCQ loading dose, FA was reported on electrocardiogram (EKG). COVID-19 treatment is leading to use off-label drugs that may generate adverse effects. It should be considered that drugs that induce QT prolongation may be triggers for atrial arrhythmias. There is not any report of sudden onset of increased QT interval with associated arrythmia after a single dose of HCQ, even in a short course treatment.

Key words: **Hydroxychloroquine, prolonged QT interval, COVID-19, atrial fibrillation, adverse drug reactions, drug interactions.**

Fibrilación auricular y prolongación del QT después de una dosis única de hidroxicloroquina

RESUMEN
Los fármacos no antiarrítmicos pueden inducir la prolongación del intervalo QT y aumentar el riesgo de arritmias. Estudios recientes han determinado que existe riesgo de desarrollar fibrilación auricular (FA) asociada a la prolongación del intervalo QT. Presentamos un caso de FA asociado a prolongación del QT secundario a una dosis única de hidroxicloroquina (HCQ) en una paciente polimedicada de 83 años ingresada en nuestro hospital por infección por SARS-CoV-2. A la paciente se le prescribió quetiapina como parte de su medicamento habitual al ingreso y se inició tratamiento frente a COVID-19 basado en HCQ oral. Treinta minutos tras la dosis de carga de HCQ, se informó FA en el electrocardiograma (ECG). El tratamiento de COVID-19 está llevando al uso de medicamentos no aprobados que pueden generar efectos adversos. Además, debe considerarse que los fármacos que inducen la prolongación del QT pueden desencadenar arritmias auriculares. No se han reportado casos de aparición repentina de aumento del intervalo QT con arritmia asociada después de una dosis única de HCQ.

Palabras clave: **Hidroxicloroquina, intervalo QT prolongado, COVID-19, fibrilación auricular, reacciones adversas a medicamentos, interacciones medicamentosas.**

INTRODUCTION

Non-antiarrhythmic drugs may induce QT-prolongation and increase the risk of arrhythmias and fatal outcome[1]. QT-interval is a marker of ventricular repolarization and its prolongation is associated with an increased risk of ventricular arrhythmia. Recent studies have established the association between atrial arrythmias and QT prolongation, determining that there is a risk of atrial fibrillation (AF) due to QT prolongation[2]. According to American Heart Association, is considering QTc prolonged interval when its value is 460 ms or longer in women and 450 ms or longer in men[3]. Hydroxychloroquine (HCQ), is a drug recently used to treat COVID-19 and know to prolong QTc interval on chronic treatment or poisoning[4,5]. We report a case of AF associated to QT prolongation secondary to a single dose of HCQ in a polymedicated patient admitted to our hospital due to SARS-CoV-2 infection.

CASE SUMMARY

An 83-year-old nursing home resident was brought to Emergency Department in May 2020 due to hypertension, discomfort and diarrhea. Medical past history included left bundle branch block, hypertension, severe dementia and Parkinson's disease. Atenolol, furosemide, memantine, co-careldopa, trazodone and quetiapine were her regular medicines. She had a previous admission in March 2020 for chest pain secondary to arterial hypertension, EKG and analytic was done (table 1).

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On admission, COVID-19 PCR test was done resulting positive. A 5-days oral HCQ regimen was started for COVID-19 based on a loading dose of 400 mg every 12 hours the first day following 200 mg every 12 hours. Further, after admission, quetiapine was prescribed as regular medicine at usual dose (100 mg every 24h).

Thirty minutes after 400 mg HCQ loading dose, the patient had an episode of hypotension and frailty. Electrocardiogram (EKG) was done and AF was reported. The ventricular rate was 130-140 beats per minute and the QTc interval was 543 ms. An increase of 13.83 % on the QTc interval was observed on EKG compared to the previous electrocardiogram in March 2020 (QTc 477ms). The patient was monitorized, troponins and electrolytes were seriated (table 1). Amiodarone perfusion was used to treat the AF. Consequently, quetiapine was stopped due to its potential interaction with HCQ in prolonging the QT interval. The day after quetiapine interruption, a new EKG was performed where it is observed a decrease in QTc of 16.02% (QTc 543 ms to 468 ms). The patient continued her COVID-19 treatment with HCQ without presenting further cardiac events and after her stabilization she was discharged to her residence.

According to Naranjo Scale a score of 7 was obtained indicating a "probable" adverse reaction to HCQ[6]. Karch and Lasagna's Algorithm to determine the causal relationship was performed resulting a score of 5 classified as "possible"[7]. To evaluate the interaction between HCQ-Quetiapine-Trazodone Horn scale was applied, a score of 5 was resulted graded as "probable"[8].

Advanced age, female gender, previous heart disease history, electrolyte disorders, and concomitant use of potential torsadogenic medicines are predisposing factors for the QT prolongation and arrythmias risk[1].

Our patient had several risk factors and was on quetiapine and trazodone as regular medicines for more than a year ago. Both drugs are classified as "Conditional Risk of TdP" drugs, according to the Arizona Center for Education and Research on Therapeutics (AzCERT). The appearance of arrythmias with these drugs is uncommon and it is usually associated with poisoning or concomitant use of QT-prolonging drugs[9].

HCQ has been used as an antimalarial for 70 years, and is now used to treat rheumatoid arthritis and systemic lupus, it have been proposed as a hopeful drug, included in numerous therapeutic protocols against SARS-CoV-2 at the beginning of the pandemic[4]. According to AzCERT HCQ is classified as "Know Risk of TdP" drug; though TdP has been reported as a HCQ uncommon adverse effect. Normally, HCQ-induced prolonged QT has been showed on chronic treatment or poisoning patients[5].

Our patient immediately experienced FA associated to QT prolongation after a single dose of HCQ as a third drug with torsadogenic properties. Due to its pharmacokinetics, HCQ is rapidly absorbed after oral administration and has been observed a lag time before absorption of 0.57 hours[10]. This may explain a timeline relationship between taking a single dose of HCQ and the onset of FA due to the additive effect with chronic quetiapine and trazodone. So far, there is not any report of sudden onset of increased QT interval with associated arrythmia after a single dose of HCQ, even in a short course treatment.

CONCLUSION

COVID-19 treatment is being a big challenge leading to use off-label drugs that may generate serious adverse effects. Further, due to the relationship between QT prolongation and AF, it should be considered that drugs that induce QT prolongation may be triggers for atrial arrhythmias. The sudden adverse reaction described highlight the need for close monitoring, especially complex patients, polypharmacy or with severe frailty who are going to take HCQ even from the first dose. This case has notified to the corresponding Pharmacovigilance Center.

Table 1. Patient's parameters and medication

	12/03/2020 (Previous admission)	19/04/2020 (HCQ admistration)	20/04/2020
Na+ (mEq/L)	135	140	142
K+ (mEq/L)	4.4	4.3	4.5
Troponin seriation (ng/L)	473-381-213	767-670-488	341
CPK (U/L)	74	-	-
HR (bpm)	85	130	68
QT (ms)	428	460	450
QTc* (ms)	477	543	468
Blood pressure (mmHg)	186/120	103/73	80/56
Sat. O2 (%)	98	98	100
QT-prolonging medication	Trazodone 50 mg/24h.	Trazodone 50 mg/24h.	HCQ 200
	Quetiapine 25 mg/ 24h.	Quetiapine 25 mg/24h. HCQ 400 mg.	mg/12h

*: Framingham Formule (Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998 May 12;97(18):1837-47. doi: 10.1161/01.cir.97.18.1837. PMID: 9603539).

Conflict of interests: The authors declare that they do not present a conflict of interest.

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